

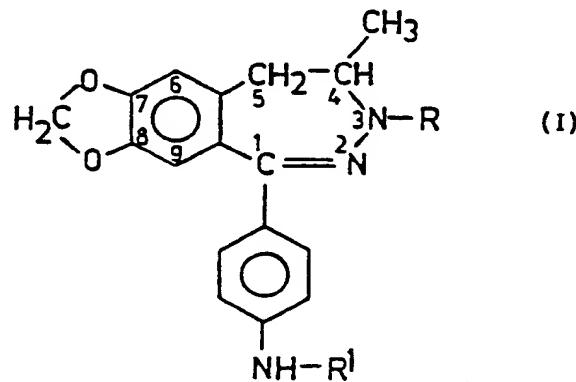


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(54) Title: 1-(4-ACYLAMINOPHENYL)-7,8-METHYLENEDIOXY-5H-2,3-BENZO-DIAZEPINE DERIVATIVES AND ACID ADDITION SALTS THEREOF, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME



(57) Abstract

The invention relates to novel compounds of general formula (I), wherein R stands for hydrogen or a C₁₋₄ alkyl group optionally substituted by a carboxyl or C₂₋₅ alkoxy carbonyl group; and R¹ means an aliphatic C₁₋₆ acyl, benzoyl or phenylacetyl group, and the stereoisomers as well as acid-addition salts of these compounds. The invention also relates to pharmaceutical compositions containing the above compounds as well as to a process for the preparation of the novel compounds of general formula (I). The compounds of the invention possess central nervous system effects, more particularly antidepressive and antiparkinsonian action. They are non-mutagenic in the Ames test. Thus, they can be useful for the treatment of depressive illnesses and parkinsonism.

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Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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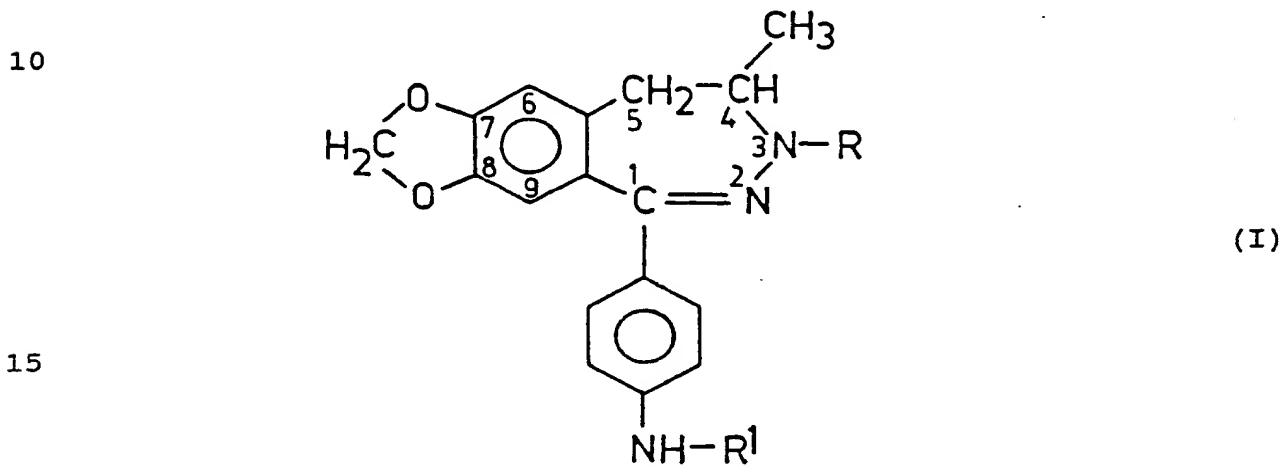
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**1-(4-ACYLAMINOPHENYL)-7,8-METHYLENEDIOXY-5H-2,3-BENZO-DIAZEPINE DERIVATIVES AND ACID ADDITION SALTS THEREOF,
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR
PREPARING SAME**

5

This invention relates to novel 1-(4-acylaminophenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivatives of the general formula (I),



wherein

R stands for hydrogen or a C₁-4 alkyl group optionally substituted by a carboxyl or C₂-5 alkoxy carbonyl group;
20 and
R¹ means an aliphatic C₁-6 acyl, benzoyl or phenylacetyl group,
as well as their acid-addition salts and pharmaceutical
25 compositions containing these compounds.

Due to the asymmetric C-4 carbon atom, the compounds of the general formula (I) can exist in the form of optically active enantiomers. The invention also relates to the race-

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mates, pure individual enantiomers and any mixture thereof.

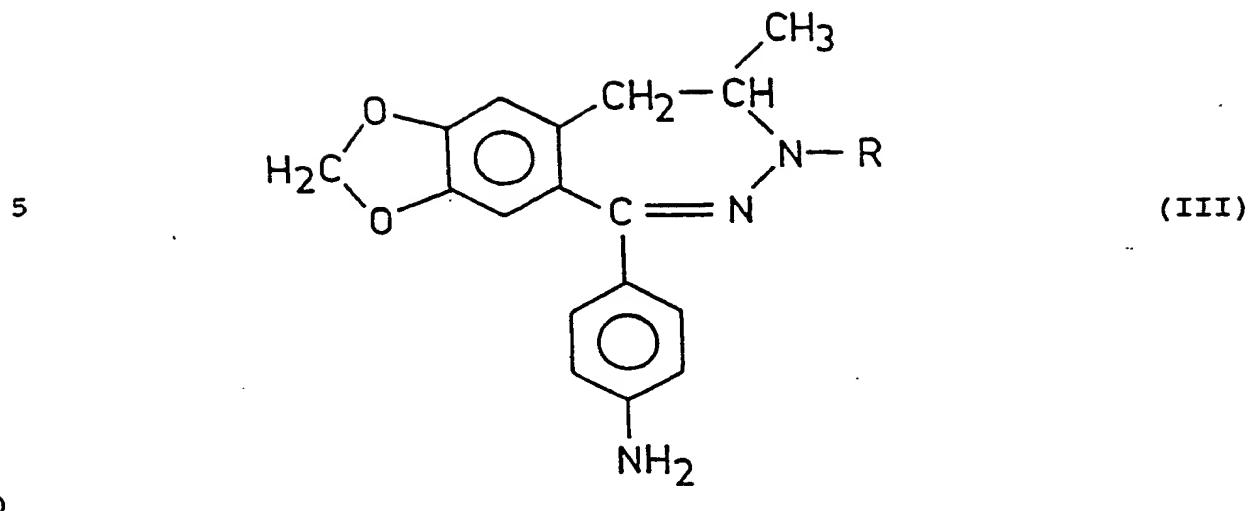
According to an other aspect of the invention, there is provided a process for the preparation of the new compounds of general formula (I) and acid addition salts thereof.

5 The aim of the present invention is to provide novel 5H-2,3-benzodiazepine derivatives possessing valuable central nervous system (CNS) effects, namely antidepressive and/or antiparkinsonian action, i.e. showing CNS-stimulating character and more advantageous properties than the 1-(4-
10 -aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see United States patent specification No. 4,835,152), the single 5H-2,3-benzodiazepine derivative known in this therapeutic area.

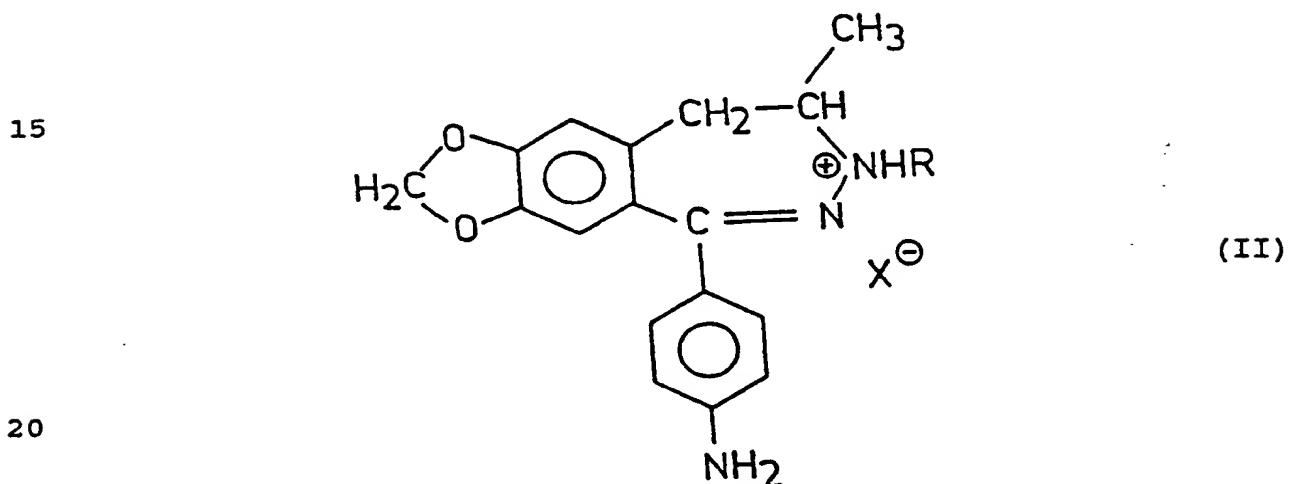
Now it has been found that the compounds of general
15 formula (I) and their acid-addition salts entirely satisfy the above demands since their effectiveness reaches that of the known compound mentioned above and, in opposition to the above compound, they proved to be non-mutagenic in the Ames-test.

20 According to the invention, the novel compounds of general formula (I) are prepared by
a₁) transforming a compound of the general formula (III)

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wherein R is as defined above, to a compound of the general formula (II),



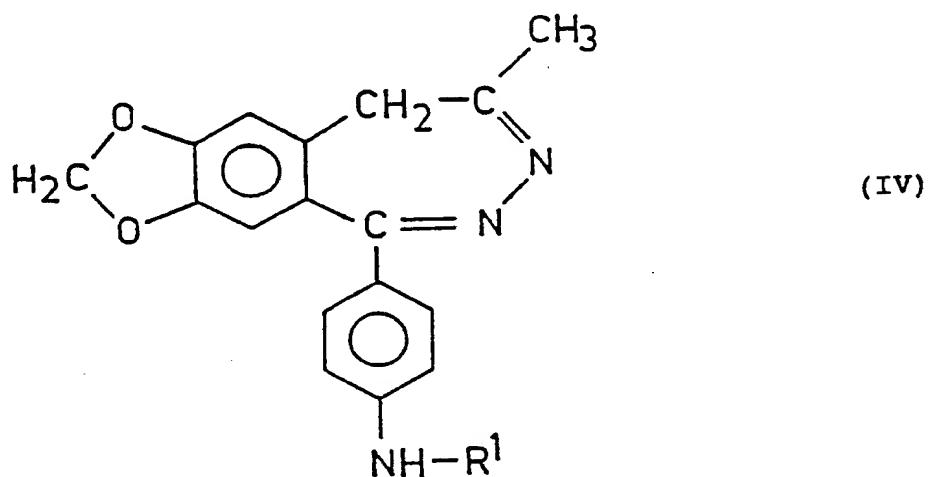
wherein R is as defined above and X means chloride, bromide, hemisulfate or methanesulfonate anion, by using an organic or inorganic acid, then acylating the product obtained, optionally without separating it, with a C₁-6 aliphatic carboxylic acid, benzoic or phenylacetic acid or a reactive derivative of these acids; or

a₂) acylating a compound of the general formula (II),

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wherein R is as defined above and X means chloride,
 bromide, hemisulfate or methanesulfonate anion, with a
₁₋₆ aliphatic carboxylic, benzoic or phenylacetic acid
 or a reactive derivative of these acids; or
 5 b) reducing a compound of the general formula (IV),

10



15

wherein R¹ is as defined above, by using an inorganic or
 inorganic-organic complex metal hydride in a suitable
 solvent, to obtain compounds of the general formula (I),
 wherein R¹ is as defined above and R means hydrogen;
 20 and, if desired, alkylating a compound of the general formula
 (I), wherein R¹ is as defined above and R stands for hydro-
 gen, prepared by using any of the above processes a₁), a₂) or
 b), with a C₁₋₄ alkyl halide optionally substituted by a C₂₋₅
 alkoxy carbonyl group or with a C₂₋₈ dialkyl sulfate in a
 25 suitable solvent, in the presence of an acid-binding agent
 and/or, if desired, hydrolyzing and then treating with an
 acid a compound of the general formula (I), wherein R¹ is as
 defined above and R stands for a C₁₋₄ alkyl group substituted

by a C₂-5 alkoxy carbonyl group, to obtain a compound of the general formula (I), wherein R stands for C₁-4 alkyl substituted by a carboxyl group and/or, if desired, converting a compound of the general formula (I) thus obtained to an acid-addition salt or, conversely, transforming a salt obtained to the corresponding free base.

According to a preferred embodiment of the process of the invention, a compound of the general formula (III), wherein R is as defined above, is transformed to a salt by 10 using an organic or inorganic acid and then the salt of the general formula (II) thus obtained, wherein R is as defined above and X represents an inorganic or organic anion, preferably chloride, bromide, hemisulfate or methanesulfonate anion, optionally without separation, is acylated with a C₁-6 15 aliphatic carboxylic, benzoic or phenylacetic acid or a reactive derivative of these acids.

In the salts of general formula (II), the quaternary nitrogen is present in the 7-membered cycle, therefore the aromatic primary amino group is free and can relatively 20 readily be acylated. The acylation can be performed in a suitable solvent or in an excess of the acylating agent. It is particularly preferable to carry out the acylation in an excess of the carboxylic acid anhydride at a temperature between 10 °C and 50 °C. This reaction lasts in general 1 to 25 5 hours.

A preferred embodiment of preparing compounds of the general formula (I), wherein R¹ is as defined above and R means hydrogen, comprises reducing a compound of the general

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formula (IV), wherein R¹ is as defined above, by using an inorganic or inorganic-organic complex metal hydride in a suitable solvent. For this selective reduction e.g. lithium aluminum hydride, sodium borohydride, potassium borohydride, 5 sodium borohydride-aluminum chloride, sodium cyanoboro-hydride, sodium dihydro-bis(2-methoxyethoxy)-aluminate, lithium trimethoxyaluminum hydride or sodium borohydride-triethyloxonium fluoborate may be used as complex metal hydrides. It is suitable to carry out the reduction in water, 10 ethers, alcohols, aromatic hydrocarbons, pyridine or a mixture thereof. The use of solvents or solvent mixtures is defined by the reducing agent used in the given case: it should be chosen in such a way that it reacts with the reducing agent very slowly if at all.

15 According to a particularly advantageous embodiment of the process of the invention, sodium borohydride is used as complex metal hydride, pyridine is employed as solvent and the reduction is suitably carried out at a temperature between 50 °C and 115 °C.

20 According to the invention, compounds of the general formula (I), wherein R stands for C₁₋₄ alkyl unsubstituted or substituted by a C₂₋₅ alkoxy carbonyl group and R¹ is as defined above, can preferably be prepared also by alkylating a compound of the general formula (I), wherein R¹ is as 25 defined above and R represents hydrogen, with a C₁₋₄ alkyl halide optionally substituted by a C₂₋₅ alkoxy carbonyl group, or with a C₂₋₈ dialkyl sulfate in a suitable solvent, preferably dimethylformamide or dimethylacetamide, in the presence

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of an acid-binding agent such as e.g. an anhydrous alkali metal carbonate or hydrogen carbonate.

Free carboxylic acids can be obtained by the hydrolysis of esters, preferably by using an alkali metal hydroxide in 5 hot 50 % ethanol and liberating the carboxylic acid from its alkali metal salt thus obtained by using an acid, preferably acetic acid.

The transformation of bases of the general formula (I) to their acid-addition salts, suitably to pharmaceutically acceptable acid-addition salts, is carried out in a known way, e.g. by dissolving or suspending the base in an appropriate solvent and adding the corresponding acid or its solution prepared in a suitable solvent. The salts are separated either directly by filtration or after evaporating the solvent; if desired, the product obtained is suspended or recrystallized and/or dried under reduced pressure.

The preparation of the compounds of general formulae (II) and (III) (wherein R is hydrogen) used as starting substances in the process according to the invention is 20 published in the United States patent specification No. 4,835,152. The compounds of general formula (IV), wherein R¹ is as defined above, are new, and are described hereinafter in the Examples.

As mentioned in the introduction, the novel compounds 25 of general formula (I) prepared by the process according to the invention possess significant central nervous system effects.

The pharmacological activity of the compounds will

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hereinafter be illustrated by results achieved in animal tests carried out by using mainly the compound of Example 1. In the comparative investigations 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine 5 (hereinafter: reference compound; see the United States patent specification No. 4,835,152) was used as reference substance which exerts similar effects but it has proven to be positive in the Ames-test on the TA-98 Salmonella strain after activation.

10 1. The behavioural effects of the compounds according to the invention were evaluated on male CFLP mice with an average body weight of 20 g (see Table 1) after oral or intraperitoneal treatment, respectively, by using Irwin's method [Psychopharmacologia, 13, 222 (1968)].

15

Table 1

Behavioural effects in mice

| | Compound (Example No.) | Doses (mg/kg) |
|----|---------------------------|------------------------------------|
| | | 100 i.p. 200 p.o. |
| 20 | Reference compound | SMA↑ stereotypy |
| | 1 | SMA↑ stereotypy |
| | 2 | transitory SMA↓ |
| 25 | 3 | φ |
| | 4 | φ |
| | 5 | φ |

The number of animals was 5 in each group.

SMA: spontaneous motor activity;

\uparrow means increase; \downarrow means decrease

ϕ : no symptom was observed

Based on the above results, behavioural effects being similar to those of the reference compound could be elicited 5 by using the compound of Example 1.

2. The effect of the compound of Example 1 on the motility in mice was more precisely analysed by means of a motimeter functioning on the basis of the capacitive resistance principle. The measurement was immediately commenced 10 after the treatment and lasted for 2 hours. The number of animals was at least 12 in each group. The percentage changes determined from the total counts during 2 hours in relation to the vehicle as control are shown in Table 2. The significance was calculated from the number of counts by using 15 Duncan's test.

Table 2
Effect on the motility in mice

| <u>Treatment</u> | <u>Doses (mg/kg) i.p.</u> | <u>Change %</u> | <u>Significance</u> |
|-----------------------|---------------------------|-----------------|---------------------|
| Reference compound | 3 | +2.8 | N.S. |
| | 10 | +90.6 | p<0.01 |
| | 30 | +318.7 | p<0.01 |
| Compound of Example 1 | 5 | +8.0 | N.S. |
| | 10 | +57.8 | p<0.05 |
| | 20 | +69.3 | p<0.05 |
| 25 | 30 | +317.3 | p<0.02 |

N.S.: not significant

It is obvious from the data of Table 2 that the motility of mice was similarly increased both by the reference compound and the compound of Example 1.

3. Investigation into the antidepressiv effect in rodents

3.1. Antagonization of reserpine hypothermia in mice

These examinations were performed in male CFLP mice by 5 using an Ellab thermometer (measurement of the rectal temperature) by the method of Askew [Life Sci. 2, 725 (1963)].

The effects of the reference compound and the compound of Example 1 are shown in Table 3. The measurement was 10 commenced after the treatment by the test substances.

Table 3

Antagonization of reserpine hypothermia in mice

| | Treatment | Doses (mg/kg) | Difference in the body temperature in relation to the reserpine control (°C) | | | | | | |
|-----------|-----------|------------------|--|--------|--------|--------|--------|--------|---------|
| | | | after | | | | | | |
| | | | 0 | 1 | 2 | 3 | 4 | 5 | 6 hours |
| 15 | Vehicle | - | +5.0 | +7.7 | +6.7 | +5.9 | +4.9 | +4.6 | +4.7 |
| Reference | 25 | -0.3 | +3.5** | +3.7** | +3.1** | +2.2** | +1.7** | +1.4** | |
| 20 | compound | 50 | -0.2 | +5.5** | +4.9** | +4.0** | +2.9** | +2.6** | +2.3** |
| Vehicle | - | +5.4 | +5.3 | +3.5 | +2.9 | +3.0 | +2.5 | +1.9 | |
| Compound | 25 | -0.3 | -0.9 | +1.3 | +2.0** | +1.7** | +0.9 | +0.8 | |
| of | 50 | -1.5* | 0 | +1.1 | +2.5** | +1.8** | +1.5** | +0.5 | |
| 25 | Example 1 | 100 | -1.8* | +0.5 | +2.6** | +4.0** | +4.1** | +2.3** | +1.2 |

*: p < 0.05

**: p < 0.01.

The hypothermic effect of reserpine was significantly antagonized by both molecules.

3.2. Porsolt's test in rats

The escape-directed fight-strengthening effects of the reference compound and the compound of Example 1 in a state of despair were investigated in male OFA rats by using 5 Porsolt's method [Eur. J. Pharmacol. 47, 379 (1978)]. The pre-selected animals were orally treated 3 times (24, 5 and 2 hours, respectively, before the measurement) with the compounds (see Table 4).

Table 4

10 **Antidepressive effect in rats (Porsolt's test)**

| | Treatment | Dose (mg/kg) | Increase in the fighting time | Significance* |
|------|--------------------------|-----------------|----------------------------------|----------------------------------|
| p.o. | | | | |
| 15 | Vehicle | - | - | - |
| | Reference compound | 10 30 | 61.6 % 159.5 % | p < 0.05 p < 0.01 |
| 20 | Vehicle | - | - | - |
| | Compound of Example 1 | 3 10 30 | 40.3 % 66.8 % 110.2 % | p < 0.05 p < 0.05 p < 0.01 |

*: Calculated from the fighting time by using Duncan's test (R.G.D. Steel and J.H. Tonie: Principles and Procedures of Statistics, 2nd Edition, p. 187, McGraw-Hill Book Co.)

25

The compound of Example 1 exerted in this test an anti-depressive effect being similar to that of the reference compound: it resulted in a significant escape-directed fight-strengthening effect even in an oral dose of 3 mg/kg.

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4. Anti-parkinsonian effect in mice [inhibition of the neurotoxicity of N-methyl-4-phenyltetrahydropyridine (abbreviated: MPTP)]

These examinations were carried out in male C57 mice
5 with an average body weight of 25 g by using the method of
Mayer et al. [J. Neurochem. 47, 1073 (1986)].

This measurement is based on the fact that MPTP, more
particularly the MPP^+ ion arising from MPTP through an
enzymatic way catalyzed by MAO-B and getting into the neuron
10 via the dopamine-uptake system, leads to the destruction of
dopaminergic cells. Thus, a status being similar to the
Parkinson's disease can experimentally be established. This
process can be prevented by compounds showing an anti-par-
kinsonian action.

15 The effect of the reference compound and compound of
Example 1 are summarized in Table 5.

Table 5
Inhibition of the MPTP neurotoxicity in mice

| 20 | Time of administration of compounds in relation to the treatment with MPTP (hour) | Reference compound Relative effect (%) $\bar{X} \pm S.E.$ | N | Compound of Example 1 | |
|----|--|---|----|--------------------------|--|
| | | | | N | Relative effect (%) $\bar{X} \pm S.E.$ |
| 25 | -4 | -8 ± 2.6 | 9 | 1 ± 4.2 | 6 |
| | -2 | 18 ± 16 | 4 | 8 ± 3.5 | 6 |
| | -1 | 28 ± 12 | 3 | 20 ± 4* | 6 |
| | -0.5 | 32 ± 6* | 12 | 37 ± 2.8* | 12 |
| | +0.5 | 61 ± 4* | 11 | 55 ± 6* | 6 |
| | +1 | 61 ± 4* | 11 | 42 ± 4.2* | 10 |
| | +2 | 43 ± 5* | 12 | 25 ± 5.2* | 4 |
| | +4 | 19 ± 4* | 17 | 11 ± 3.4 | 11 |
| | +6 | 6 ± 1.8 | 12 | 1 ± 1.3 | 6 |

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*: Significant difference in relation to the MPTP control

N: number of animals

Doses: 2 x 30 mg/kg i.p.

$$\text{Relative effect (\%)} = \frac{\text{DA level}_{(\text{MPTP+compound})} - \text{DA level}_{(\text{MPTP})}}{100 - \text{DA level}_{(\text{MPTP})}} \times 100$$

DA: 'dopamine

According to the data of Table 5 both the reference compound and the compound of Example 1 significantly reduce the dopamine-level decrease induced by the treatment with MPTP. This effect of both compounds appear under the effect of treatments both before and after administration of MPTP.

Biochemical investigations were carried out in order to
15 elucidate the action mechanism functioning in the anti-
depressive and anti-parkinsonian as well as stimulatory
effects of the compound of Example 1 and appearing in the
pharmacological investigations.

The direct dopamine receptor-binding studies gave
20 negative results.

5. Inhibition of the dopamine and MPP⁺ uptake

These examinations were carried out on a raw synaptosome preparation from the striatal tissue of the rat brain according to Schacht and Hepter [Biochem. Pharmacol. 12, 25 3412 (1974)] or Javitch and Snyder [Eur. J. Pharmacol. 106, 455 (1985)], respectively. The results are summarized in Table 6.

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Table 6
The in vitro inhibition of dopamine and MPP⁺ uptake

| Compound | IC ₅₀ (M) | |
|-----------------------|------------------------|------------------------|
| | Dopamine | MPP ⁺ |
| Reference compound | 7.6 × 10 ⁻⁶ | 2.8 × 10 ⁻⁶ |
| Compound of Example 1 | 8.3 × 10 ⁻⁶ | 8.8 × 10 ⁻⁶ |

The reference compound and the compound of Example 1 inhibit the dopamine and MPP⁺ uptake into the neuron with the same effectiveness. The pharmacological activity can be explained by this biochemical effect.

15 6. Other central nervous system effects

These measurements were performed in male CFLP mice with a body weight of 20 g.

For the examination of the narcosis-potentiating effect, the animals were orally treated with the test substances and 30 minutes later they received an intravenous dose of 50 mg/kg of hexobarbital inducing narcosis. The prolongation of the duration of narcosis was measured in relation to the vehicle control group.

For investigation of the anticonvulsive effect, a tonic-clonic seizure was induced by electric current (10 mA, 2 sec, 0.4 msec) after 1-hour oral pretreatment. The ceasing of tonic extension of the hind legs was evaluated as an anticonvulsive effect [Swinyard: J. Pharm. Exp. Ther. 106, 319

(1952)]. The results are summarized in Table 7.

Table 7

Other central nervous system effects on mice

| Compound | | Anticonvulsive effect (ES) oral ED ₅₀ * (mg/kg) | Narcosis-potentiating effect after an oral dose of 50 mg/kg |
|----------|--------------------|--|---|
| 5 | Reference compound | 52 (39.7-68.1) | 479 % |
| 10 | 1 | 195 (159.8-237.9) | 68 % |
| | 2 | 98 (77.8-123.5) | 159 % |
| | 3 | > 100 | 232 % |
| 15 | 4 | > 100 | 159 % |
| | 5 | > 100 | 152 % |

*: Calculated by using probit analysis

ES: electric seizure (electroshock)

20 None of the tested molecules reached the anticonvulsive and narcosis-potentiating effect of the reference compound; however, the compounds of Examples 1 and 2 showed a considerable activity in the anticonvulsive test.

7. Acute toxicity in mice

25 The approximating LD₅₀ values of the compound of Example 1 (after a single treatment with an observation period of 14 days) are as follows:

Oral LD₅₀: > 500 mg/kg

Intraperitoneal LD₅₀: ≈ 150 mg/kg

Summing up, it can be stated that, among the compounds according to the invention, the compound of Example 1 shows

in rodents an antidepressive and anti-parkinsonian effect of the same order as the reference compound. The mechanism of action of both molecules is the same: they selectively inhibit the dopamine uptake (and simultaneously the MPP⁺) system.

Considering that cerebral depaminergic systems play an actual and essential role in the motivated behaviour, it may be hoped that molecules acting on this system would show a considerable antidepressive effect in man. This supposition is supported by several drug candidates possessing a similar biochemical mechanism of action with a positive effect in man, such as e.g. bupropion [chemically (\pm)-2-tert-butyl-amino-3'-chloropropiophenone hydrochloride] or amineptine [chemically 7-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)aminoheptenoic acid hydrochloride].

On the other hand, the advantageous effect in the MPTP model of the compound of Example 1, which is similar to that of the reference compound (MPTP induces Parkinson's disease in man, too), indicates the possibility of a human anti-parkinsonian effectivity.

On the basis of the above pharmacological results, the compounds of the invention can be used for treating depressive conditions and parkinsonism.

For therapeutical use, an indicated oral daily dose is in the range from about 0.05 mg/kg to about 20 mg/kg, preferably from 0.1 mg/kg to 10 mg/kg, more preferably 1 mg/kg.

For therapeutical use, the active compounds of the invention are suitably formulated to pharmaceutical composi-

tions by mixing them with nontoxic, inert solid or liquid carriers and/or additives, which are suitable for enteral or parenteral administration and are commonly used in the pharmaceutical industry. Suitable carriers are e.g. water, 5 gelatin, lactose, starch, pectin, magnesium stearate, stearic acid, talc and vegetable oils. As additives preservatives, wetting (surface-active), emulsifying or dispersing, buffering and aromatizing agents may be used.

By using the above carriers and additives, the active 10 compounds of the invention may be formulated to the usual pharmaceutical compositions, e.g. solid forms (such as mainly tablets, dragées and capsules) as well as to injectable solutions, suspensions and emulsions.

The invention also relates to pharmaceutical 15 compositions containing a compound of the general formula (I) or a pharmaceutically acceptable acid-addition salt thereof as active ingredient as well as to a process for preparing these compositions.

The compositions according to the invention can be 20 prepared by commonly known methods.

The invention also relates to a method for treating depressive illnesses and Parkinson's disease. This method comprises administering a therapeutically effective amount of an active ingredient of the general formula (I) to the 25 patient in need of such treatment.

The identification of compounds of the invention was performed by elementary analysis; their purity and structure were proven by thin-layer chromatography (TLC) as well as by

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their IR, $^1\text{H-NMR}$ and mass spectra. The date of analysis were in accordance with the empirical formula within the limits of error.

The invention is further illustrated by the following 5 non-limiting Examples.

Example 1

**1-(4-Acetylaminophenyl)-4-methyl-7,8-methylenedioxy-
-3,4-dihydro-5H-2,3-benzodiazepine**

Method A)

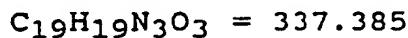
10 To a solution containing 6.0 g (20 mmol) of 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see United States patent specification No. 4,835,152) in 30 ml of ethyl acetate 1.38 ml (21 mmol) of methanesulfonic acid were added. The crystalline precipitate 15 was filtered and washed with 5 x 5 ml of ethyl acetate. The dry weight of the product was 7.37 g, m.p.: it sintered above 190 °C and weakly decomposed at 210-212 °C. The thus-obtained methanesulfonate salt of the starting substance could be acetylated as follows:

20 7.37 g of the powdered salt were suspended in 110 ml of acetic anhydride, the suspension was stirred at room temperature for 2 hours, then the crystalline precipitate was filtered, washed with 5 x 10 ml of ethyl acetate and dried to give 6.54 g of methanesulfonate salt of the target compound, 25 m.p. 240-241 °C (with decomposition).

The base could be liberated from the methanesulfonate salt of the target compound e.g. in the following way: 6.54 g of salt were dissolved in 90 ml of water, the solution was

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clarified by charcoal, then 3.6 g of sodium hydrogen carbonate were portionwise added to the clear solution. The precipitate was filtered, washed with 5 x 10 ml of water and dried to obtain 5.54 g of crude product. After recrystallization from 130 ml of isopropanol, 3.11 g (yield 46 %) of product were obtained, m.p.: 221-223 °C (weak decomposition), the melting point of which was increased to 223-225 °C after digesting with 15 ml of hot benzene.



10 The hydrochloride salt decomposed at 262-264 °C.

Method B)

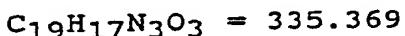
After dissolving 15.0 g (44.7 mmol) of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 150 ml of pyridine under mild heating, 10.2 g (0.269 mol) of sodium borohydride were added and the mixture was stirred on an oil bath of 100 °C temperature for 5 hours. Then the reaction mixture was cooled to about 25 °C, 150 ml of water were dropwise added under continuous stirring during 20 minutes, thereafter a mixture containing 180 ml of concentrated hydrochloric acid and 265 ml of water was added while cooling by ice-water. A yellowish suspension was formed. The precipitate was filtered, washed with 5 x 20 ml of water and dried to yield 15.2 g of salt, m.p. above 250 °C. In order to liberate the base, this salt was suspended in 150 ml of 50 % ethanol, 5.7 g of sodium hydrogen carbonate were portionwise added while stirring, then the suspension was filtered after 30 minutes, washed successively with 3 x 10 ml of 50 % ethanol, with 5 x 20 ml of water, finally

- 20 -

with 20 ml of 50 % ethanol and dried to obtain 10.95 g of a crude product, m.p.: 218-220 °C (weak decomposition). After digesting this crude product with 50 ml of hot isopropanol and then with 100 ml of hot 99.5 % ethanol, 8.63 g (57.2 %) of the aimed compound were obtained, m.p.: 220-222 °C (weak decomposition).

The starting substance was prepared as follows.

10 g (34 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were stirred for 3 hours with 100 ml of acetic anhydride. The crystals formed were filtered, washed with 5x10 ml of anhydrous ethanol and dried, to yield 9.2 g of raw product, m.p.: 252-254 °C (decomposition). This product was treated with 45 ml of hot 99.5 % ethanol. After cooling the crystals were filtered, washed with 3x10 ml of ethanol and dried to obtain 8.68 g (76.1 %) of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine, m.p.: 256-258 °C.



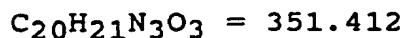
Example 2

20 1-(4-Propionylaminophenyl)-4-methyl-7,8-methylenedioxy-
 -3,4-dihydro-5H-2,3-benzodiazepine

Method A)

After adding 1.70 g (4.3 mmol) of powdered 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine methanesulfonate to 10 ml of propionic acid anhydride, the reaction mixture was stirred at 20 °C for 2.5 hours. The precipitated salt was washed with 4 x 5 ml of ethyl acetate and dried to give 1.86 g of product, m.p.:

246-248 °C (decomposition). The base was liberated as described in Method A) of Example 1 to obtain 1.36 g of product, m.p.: 226-233 °C (weak decomposition). The melting point of this product was increased to 237-239 °C after re-
5 crystallization from 40 ml of 99.5 % ethanol to give the aimed compound in a yield of 1.8 g (71.5 %).

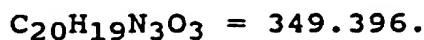


The same product was obtained with a yield of 65 % by adding first 2.15 mmol of concentrated sulfuric acid, then
10 4.3 mmol of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-
-3,4-dihydro-5H-2,3-benzodiazepine base to the propionic acid anhydride and otherwise working as described above.

Method B)

When starting from 1.65 g (4.72 mmol) of 1-(4-
15 -propionylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-
-benzodiazepine and otherwise following Method B) of Example 1 (except that alkalinization was carried out by using 40 % aqueous sodium hydroxide solution and the extraction was performed by using benzene) and recrystallizing the crude
20 product from ethanol, 1.2 g (72.3 %) of the aimed product were obtained, m.p.: 235-236 °C (weak decomposition).

1-(4-Propionylaminophenyl)-4-methyl-7,8-methylenedioxy-
-5H-2,3-benzodiazepine used as starting substance was prepared in the same way as described above for the 4-acetyl-
25 amino analogue, except that propionic acid anhydride was used instead of acetic acid anhydride, m.p.: 228-230 °C (decomposition).



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Examples 3 to 5

The compounds of Examples 3 to 5 were also prepared as described in Method B) of Example 1.

Example 3

5 1-(4-Benzoylaminophenyl)-4-methyl-7,8-methylenedioxy-
-3,4-dihydro-5H-2,3-benzodiazepine

$C_{24}H_{21}N_3O_3 = 399.456$; it decomposes at 247-248 °C.

The 1-(4-benzoylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine used as starting substance was 10 obtained as follows.

1.0 ml (15 mmol) of benzoyl chloride and 2.1 ml (15 mmol) of triethylamine were added to a solution of 4 g (13.6 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in dichloromethane and the reaction mixture was stirred at 25 °C for 24 hours. The solution was extracted with 3x30 ml of water, 3x20 ml of a 4 % aqueous sodium hydroxide solution and finally with 2x30 ml of distilled water. The organic layer was dried, evaporated at reduced pressure, then the crystalline residue was treated with 20 ml of hot ethanol to yield 3.97 g of raw product, m.p.: 242-243 °C. This raw product was repeatedly treated with 20 ml of hot ethanol, next day it was filtered at 0-5 °C, washed with 3x3 ml of ethanol and dried at 100 °C to obtain 3.85 g (71.3%) of a pure product, m.p.: 246-247 °C 25 (decomposition).

$C_{24}H_{19}N_3O_3 = 397.40$

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Example 4

4-Methyl-7,8-methylenedioxy-1-(4-phenylacetylaminophenyl)-3,4-dihydro-5H-2,3-benzodiazepine

$C_{25}H_{23}N_3O_3 = 413.483$; it decomposes at 213-215 °C.

5 The 4-methyl-7,8-methylenedioxy-1-(4-phenylacetylaminophenyl)-5H-2,3-benzodiazepine used as starting substance was prepared in the following way.

After adding 0.7 g (3.4 mmol) of DCC and 0.46 g (3.4 mmol) of phenylacetic acid to the solution of 0.5 g (1.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 30 ml of anhydrous methylene chloride, the mixture was stirred at 25 °C for 48 hours and filtered. The precipitate was combined with the evaporation residue of the filtrate and purified by chromatography on silica gel, by 15 using a 4:1 mixture of ethyl acetate-methanol as eluent. The fractions containing the aimed product were evaporated, the residue was boiled with 5 ml of ethanol, cooled down and filtered to obtain 0.60 g (87.72 %) of the aimed product, m.p.: 245-247 °C (decomposition).

20 **Example 5**

4-Methyl-7,8-methylenedioxy-1-(4-pivaloylaminophenyl)-3,4-dihydro-5H-2,3-benzodiazepine

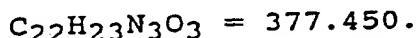
$C_{22}H_{25}N_3O_3 = 379.466$; it decomposes at 134-136 °C.

The 4-methyl-7,8-methylenedioxy-1-(4-pivaloylaminophenyl)-5H-2,3-benzodiazepine used as starting substance was prepared in the following manner.

1.56 ml (11.2 mmol) of triethylamine and 1.38 ml (11.2 mmol) of pivaloyl chloride were added to a solution of 3 g

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(10.2 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-
 -5H-2,3-benzodiazepine in 160 ml of dichloromethane and the
 reaction mixture was stirred at 25 °C for one hour. The
 precipitate formed was filtered, washed with 3x5 ml of di-
 5 chloromethane, then with 3x20 ml of water and dried to give
 1.59 g of the pure product, m.p. 225-227 °C (decomposition).
 The other portion of the product was isolated from the
 organic phase. The filtrate was extracted with 3x20 ml of
 water, then with 3x15 ml of 4 % aqueous sodium hydroxide
 solution, finally with 2x30 ml of water. The organic layer
 10 was subsequently dried and evaporated under reduced pressure.
 The crystalline residue was combined with the former 1.59 g
 of the product and suspended in 20 ml of hot ethanol. The
 product was filtered after cooling, washed with 3x3 ml of
 15 ethanol and dried to obtain 3.38 g (87.8 %) of the pure
 product, m.p.: 225-227 °C.



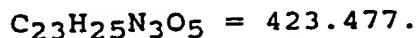
Example 6

20 1-(4-Acetylaminophenyl)-3-ethoxycarbonylmethyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.26 g (3.7 mmol) of the target compound of Example 1 were dissolved in 5 ml of pure dimethylformamide, then 0.51 g (3.7 mmol) of potassium carbonate (anhydritized by heating) and 25 0.42 ml (3.7 mmol) of ethyl bromoacetate were added while stirring. The reaction mixture was stirred at room temperature for 6 hours. Next day the crude product was precipitated by adding 50 ml of water. After filtration, washing with

- 25 -

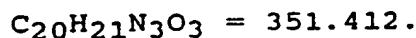
5 x 4 ml of water and drying, the crude product weighed 1.36 g. This product was purified by column chromatography on Kieselgel GO by using a 4:1 ethyl acetate/benzene mixture for elution. After recrystallization from 10 ml of 50 % ethanol, 5 1.05 g (67 %) of the aimed product were obtained, m.p.: 156-157 °C.



Example 7

10 **1-(4-Acetylaminophenyl)-3,4-dimethyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

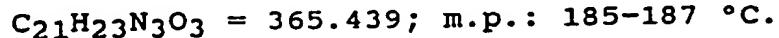
The process described in Example 6 was followed, except that methyl iodide was used instead of ethyl bromoacetate, the column chromatography was omitted and the crude product was recrystallized first from 50 % and then from 99.5 % 15 ethanol to give the pure aimed compound, m.p.: 207-209 °C.



Example 8

1-(4-Acetylaminophenyl)-3-ethyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

20 The process described in Example 7 was followed, except that ethyl iodide was used instead of methyl iodide and the recrystallization was carried out with 50 % ethanol.



Example 9

25 **1-(4-Acetylaminophenyl)-3-carboxymethyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine**

0.59 g (1.4 mmol) of the compound of Example 6 was boiled with 15 ml of 50 % ethanol and 0.10 g (1.8 mmol) of

potassium hydroxide under reflux for 30 to 40 minutes. After cooling 0.15 ml (2.5 mmol) of acetic acid was added to the filtered, clear solution to liberate the free carboxylic acid which was then separated by filtration after cooling. The 5 acid was washed with 4 x 2 ml of 50 % ethanol and then with 3 x 3 ml of water and dried to obtain 0.45 g (81.3 %) of the aimed product which sintered from 162 °C and weakly decomposed at 164-166 °C.



10 **Example 10**

Preparation of pharmaceutical compositions

a) Divided (grooved) tablets containing 25 mg of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Example 1)

15 **Ingredients of one tablet:**

| | | |
|----|--|----------|
| | Active ingredient | 25.0 mg |
| | Magnesium stearate | 0.5 mg |
| | Stearin | 0.5 mg |
| | Talc | 1.0 mg |
| 20 | Gelatin | 1.7 mg |
| | Microcrystalline cellulose | 5.0 mg |
| | Maize starch | 10.3 mg |
| | Lactose | 46.0 mg. |
| | b) Dragées containing 12.5 mg of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine | |

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Ingredients of one dragée-core:

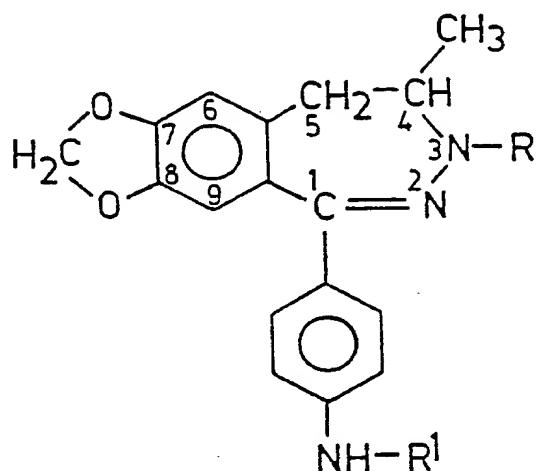
| | | |
|---|----------------------|----------|
| | Active ingredient | 12.5 mg |
| | Magnesium stearate | 1.0 mg |
| | Polyvinylpyrrolidone | 5.0 mg |
| 5 | Maize starch | 16.0 mg |
| | Lactose | 38.0 mg. |

The dragée-core was coated with sugar and talc in the usual way and then polished by using bee-wax. Each dragée weighed about 100 mg.

Claims

1. 1-(4-Acylaminophenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivatives of the general formula (I),

5



(I)

10

wherein

15 R stands for hydrogen or a C₁-4 alkyl group optionally substituted by a carboxyl or C₂-5 alkoxy carbonyl group; and
 R¹ means an aliphatic C₁-6 acyl, benzoyl or phenylacetyl group,

20 and their stereoisomers and acid-addition salts.

2. 1-(4-Acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine.

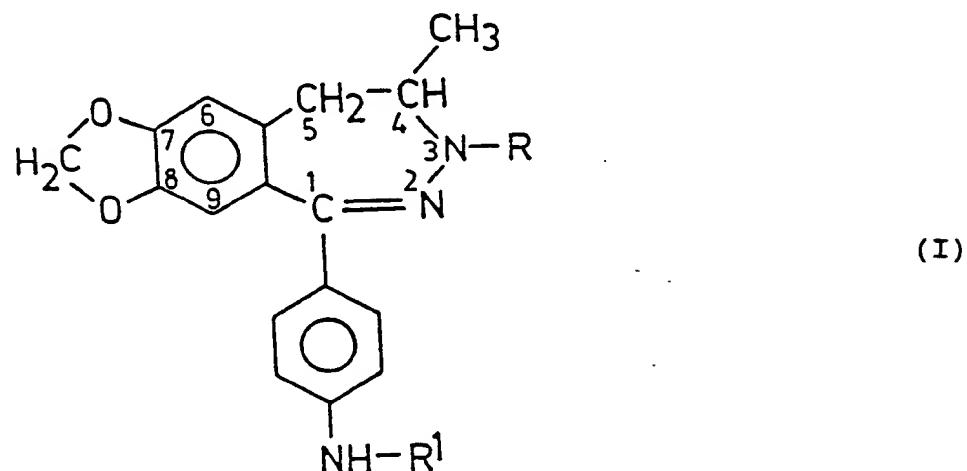
3. A pharmaceutical composition, which comprises as active ingredient a novel 1-(4-acylaminophenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivative of the general formula (I), wherein R and R¹ are as defined in claim 1, or a pharmaceutically acceptable acid-addition salt thereof in admixture with carriers and/or additives commonly

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used in the pharmaceutical industry.

4. A process for the preparation of novel 1-(4-
-acylamino-phenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine
derivatives of the general formula (I),

5



10

wherein

15 R stands for hydrogen or a C₁₋₄ alkyl group optionally substituted by a carboxyl or C₂₋₅ alkoxy carbonyl group; and

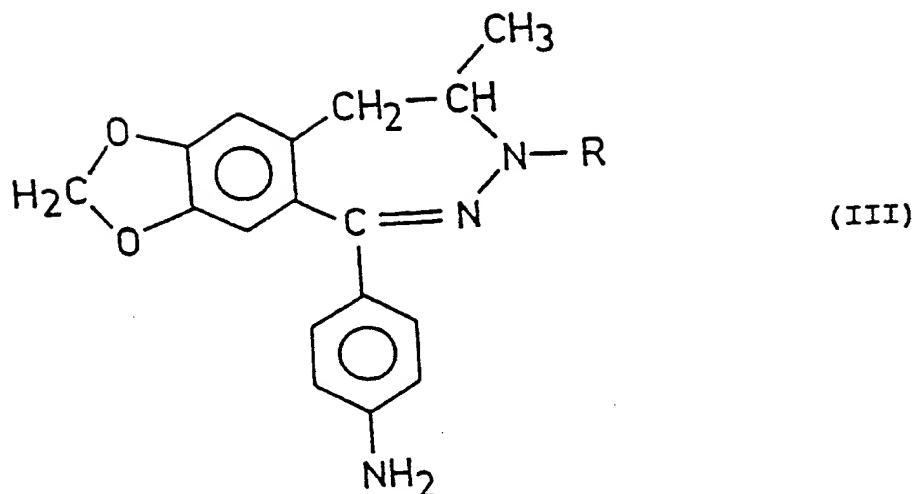
R¹ means an aliphatic C₁₋₆ acyl, benzoyl or phenylacetyl group,

20 and their stereoisomers as well as acid-addition salts, which comprises

a₁) transforming a compound of the general formula (III)

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5

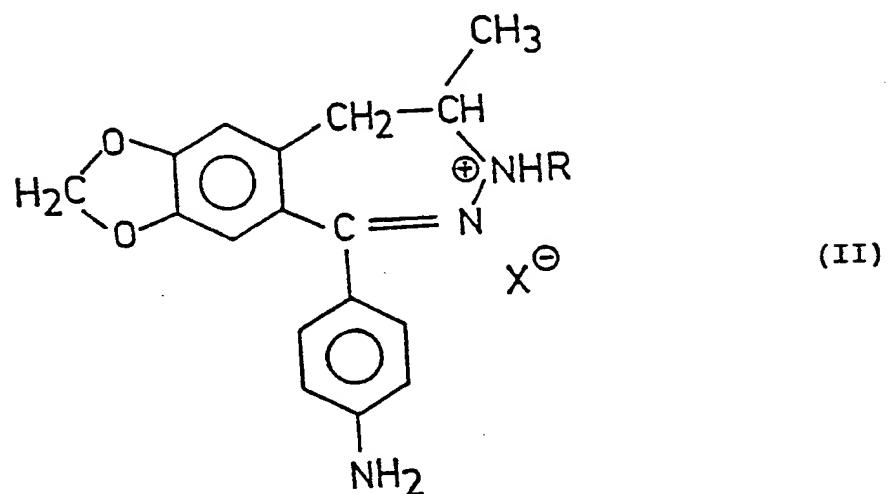


10

wherein R is as defined above, to a compound of the general formula (II),

15

20



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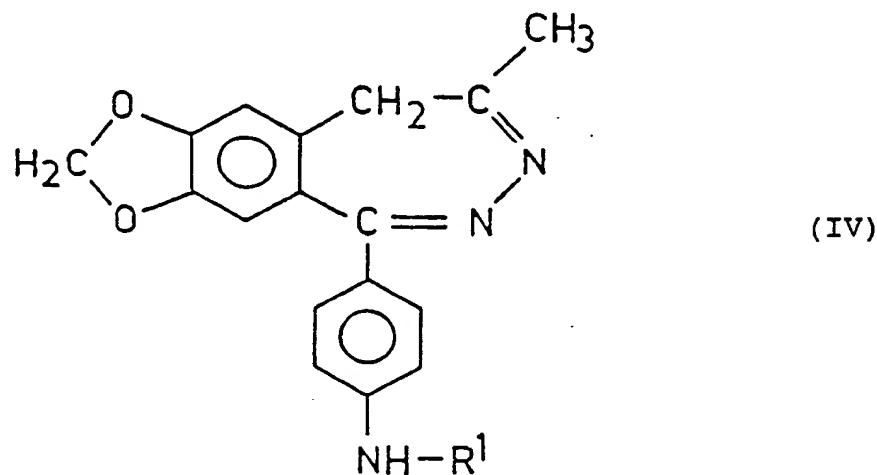
wherein R is as defined above and X means chloride, bromide, hemisulfate or methanesulfonate anion, by using an organic or inorganic acid, then acylating the product obtained, optionally without separating it, with a C₁-6 aliphatic carboxylic acid, benzoic or phenylacetic acid or a reactive derivative of these acids; or

a₂) acylating a compound of the general formula (II),

wherein R is as defined above and X means chloride, bromide, hemisulfate or methanesulfonate anion, with a C₁₋₆ aliphatic carboxylic, benzoic or phenylacetic acid or a reactive derivative of these acids; or

5 b) reducing a compound of the general formula (IV),

10



15

wherein R¹ is as defined above, by using an inorganic or inorganic-organic complex metal hydride in a suitable solvent, to obtain compounds of the general formula (I), wherein R¹ is as defined above and R means hydrogen;

20 and, if desired, alkylating a compound of the general formula (I), wherein R¹ is as defined above and R stands for hydrogen, prepared by using any of the above processes a₁), a₂) or b), with a C₁₋₄ alkyl halide optionally substituted by a C₂₋₅ alkoxycarbonyl group or with a C₂₋₈ dialkyl sulfate in a
 25 suitable solvent, in the presence of an acid-binding agent and/or, if desired, hydrolyzing and then treating with an acid a compound of the general formula (I), wherein R¹ is as defined above and R stands for a C₁₋₄ alkyl group substituted

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by a C₂-5 alkoxy carbonyl group, to obtain a compound of the general formula (I), wherein R stands for C₁-4 alkyl substituted by a carboxyl group and/or, if desired, converting a compound of the general formula (I) thus obtained to an acid-5 addition salt or, conversely, transforming a salt obtained to the corresponding free base.

5. A process as claimed in claim 4, process a₁) or a₂), which comprises carrying out the acylation with the corresponding carboxylic acid anhydride, preferably in an 10 excess of the carboxylic acid anhydride, at a temperature between 10 °C and 50 °C during 1 to 5 hours.

6. A process as claimed in claim 4, process b), which comprises using lithium aluminum hydride, sodium borohydride, potassium borohydride, sodium borohydride/aluminum chloride, 15 sodium cyanoborohydride, sodium bis(2-methoxyethoxy)aluminum hydride, lithium trimethoxyaluminum hydride or sodium boro-hydride/triethyloxonium fluoborate and carrying out the reduction in a solvent or solvent mixture which is non-reacting or slowly reacting to the complex metal hydride employed.

20 7. A process as claimed in claim 6, which comprises carrying out the reduction with sodium borohydride in pyridine.

8. A process as claimed in claim 4, which comprises carrying out the alkylation in dimethylformamide, in the 25 presence of an anhydrous alkali metal hydrogen carbonate or carbonate as acid-binding agent.

9. A process as claimed in claim 4, which comprises carrying out the selective hydrolysis of compounds of the

general formula (I), containing as R a C₁₋₄ alkyl group substituted by a C₂₋₅ alkoxy carbonyl group, by using an alkali metal hydroxide in hot 50 % ethanol and liberating the free carboxylic acid derivative by acetic acid.

5 10. A process for the preparation of a pharmaceutical preparation, which comprises mixing as active ingredient a novel 1-(4-acylaminophenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivative of the general formula (I), wherein R and R¹ are as defined in claim 1, or a pharmaceutically acceptable acid-addition salt thereof, prepared by using any of processes a₁) to b) claimed in claim 4, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

11. Method for treating mammals (including man) suffering from a depressive illness or Parkinson's disease, which comprises administering a therapeutically effective amount of an 1-(4-acylaminophenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivative of the general formula (I), wherein R and R¹ are as defined in claim 1, or a pharmaceutically acceptable acid-addition salt thereof, to a subject in need of such treatment.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 91/00053

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.⁵: C 07 D 491/056 // (C 07 D 491/056, 317:00, 243:00)

II. FIELDS SEARCHED

Minimum Documentation Searched 7

| Classification System | Classification Symbols |
|-----------------------|------------------------|
| Int.Cl. ⁵ | C 07 D 491/056 |

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT*

| Category * | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ |
|------------|--|-------------------------------------|
| D, A | US, A, 4 835 152 (KORÖSI et al.) 30 May 1989 (30.05.89), see claims 1-7. | 1-4, 10 |
| A | US, A, 4 423 044 (KORÖSI et al.) 27 December 1983 (27.12.83), see abstract. | 1 |
| | ----- | |

* Special categories of cited documents:¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

IV. CERTIFICATE

Date of the Actual Completion of the International Search

25 March 1992 (25.03.92)

Date of Mailing of this International Search Report

01 April 1992 (01.04.92)

International Searching Authority

AUSTRIAN PATENT OFFICE

Signature of Authorized Officer

Veličković - Heine

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹**

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:
 1. Claim numbers 11..... because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

ANHANG**ANNEX****ANNEXE**

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

to the International Search Report to the International Patent Application No.

au rapport de recherche international relatif à la demande de brevet international n°

PCT/HU91/00053

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalem Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Orientierung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office.

| Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche | Datum der Veröffentlichung Publication date Date de publication | Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets | Datum der Veröffentlichung Publication date Date de publication |
|---|---|--|--|
| US A 4835152 | 30-05-89 | AU A1 76880/87 AU B2 596206 BE AE 1002415 CA A1 1284322 CH A 673652 CS A2 8706007 CS B2 264150 DD A5 265627 DE A1 3727226 DK A0 4248787 DK A 4248/87 ES AF 2004985 FI A0 873525 FI A 873525 FI B 85706 FR A1 2602770 FR B1 2602770 GB A0 8719265 GB A1 2194236 GB B2 2194236 HU A2 47287 HU B 198494 IT A0 8721667 JP A2 63099073 NL A 8701909 NO A0 873426 NO A 873426 NO B 164656 NO C 164656 PL A1 276326 PL B1 148536 SE A0 8703169 SE A 8703169 YU A 1514/87 | 18-02-88 26-04-90 05-02-91 21-05-91 30-03-90 16-08-88 13-06-89 08-03-89 18-02-88 14-08-87 16-02-88 16-02-89 14-08-87 16-02-88 14-02-92 19-02-88 02-11-90 07-09-87 02-03-88 21-03-90 28-02-89 30-10-89 14-08-87 20-04-88 01-03-88 14-08-87 16-02-88 23-07-90 31-10-90 21-07-88 31-10-89 14-08-87 16-02-88 31-12-88 |
| US A 4423044 | 27-12-83 | AT A 969/82 AT B 383120 AU A1 81308/82 AU B2 550388 BE A1 892395 CA A1 1178584 CH A 648553 CS P 224646 DD A5 204698 DE A1 3209100 DK A 1068/82 EE A1 510348 EE A5 510348 FI A1 8302671 FI A 820839 FR A1 2501686 FR B1 2501686 GB A1 2097387 GB B2 2097387 HU B 186760 IL A1 65076 IT A0 8220094 IT A 1190732 JP A2 57159772 NL A 8201005 NO A 820798 SE A 8201537 SU A3 1151206 | 15-10-86 25-05-87 16-09-82 20-03-88 08-09-82 27-11-84 29-03-85 16-01-84 07-12-82 28-10-82 13-09-82 01-02-83 26-02-83 16-04-83 15-09-82 17-09-82 01-03-82 03-11-82 19-09-84 30-09-85 31-12-84 11-03-82 24-02-88 01-10-82 01-10-82 13-09-82 13-09-82 16-04-85 |